DOI:
10.1007/s40473-020-00200-x

Document Version
Publisher's PDF, also known as Version of record

Current Behavioral Neuroscience Reports
https://doi.org/10.1007/s40473-020-00200-x

BIPOLAR DISORDER (J SOARES AND M SANCHES, SECTION EDITORS)

The Treatment of Bipolar Depression: Current Status and Future Perspectives

Luke A. Jelen [1,2] · Allan H. Young [1,2]

Abstract

Purpose of Review This paper aims to review current available treatment options and to consider future directions in the treatment of bipolar depression.

Recent Findings There are a limited number of established treatments that have demonstrated varied efficacy in acute bipolar depression including modern antipsychotics (quetiapine, lurasidone, olanzapine ± fluoxetine and recently cariprazine) and mood stabilisers (lamotrigine and valproate). Lithium has a role in protecting against depressive relapses and suicide. Alternative and experimental treatments including pramipexole, modafinil/armodafinil, omega-3 fatty acids and thyroxine may be used to augment the treatment of bipolar depression. Ketamine represents a major breakthrough, producing rapid reductions in depressive symptoms even in cases of treatment-resistance, but challenges remain in how best to maintain response and reduce unwanted side effects.

Summary There remains uncertainty with regard to the relative efficacy and safety of established and experimental treatments for bipolar depression. Further work using consistent, optimal trial designs as well as further investigation into novel compounds and treatment interventions is warranted.

Keywords Bipolar disorder · Bipolar depression · Antidepressants · Mood stabilisers · Antipsychotics · Experimental treatments

Introduction

Bipolar disorder is a disabling condition characterised by recurrent episodes of depression and mood elevation (mania or hypomania) and mixed states. With respect to symptom duration, depression is typically the predominant phase in bipolar disorder [1], accounting for a greater proportion of impaired social and occupational functioning, morbidity and an excess mortality associated with suicide [2, 3].

Bipolar depression poses a therapeutic challenge, complicated by the need to relieve depressive symptoms without precipitating mania, hypomania or worsening cycle frequency [4]. Despite its high prevalence and clinical importance, until recently there have been relatively few randomised controlled trials (RCTs) in bipolar depression. Although there are a limited number of established treatments demonstrating efficacy in acute episodes, there is a paucity of evidence to decide between different agents and the therapeutic, prophylactic or harmful effects in the long term are less well evaluated.

Bipolar I and II are the most commonly diagnosed subtypes of bipolar disorder. For a diagnosis of bipolar I, criteria must have been met for at least one manic episode which may have been preceded and may be followed by major depressive episodes. To qualify for a diagnosis of bipolar II, the individual must have had at least one hypomanic and at least one major depressive episode [5]. Relative to bipolar I, there has been less research on the safety and efficacy of pharmacological treatments in bipolar II disorder and specifically bipolar II depression [6]. Only a limited number of agents have been examined in both.

This article is part of Topical Collection on *Bipolar Disorder*

✉ Luke A. Jelen
luke.jelen@kcl.ac.uk

[1] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

[2] South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Monks Orchard Road, Beckenham, Kent BR3 3BX, UK

Published online: 15 January 2020

Here, we first review current evidence for recognised treatments in bipolar depression before exploring alternative and experimental treatment options. Finally, we summarise our findings and discuss limitations in this field of research before considering future perspectives in the treatment of bipolar depression.

Antidepressants

Although antidepressants are commonly prescribed for bipolar depression, their use remains controversial [7]. There is a particular lack of placebo-controlled, monotherapy trials examining efficacy of antidepressants in bipolar depression with notable concerns regarding the risk of mood activation, causing a switch to mania or inducing rapid cycling, with the use of 'unopposed' antidepressants (i.e. without mood stabiliser or antipsychotic protection).

Two large placebo-controlled trials provided evidence to suggest a potential lack of efficacy of antidepressants in the treatment of bipolar depression. The first, an add-on study, found no additional benefit from adjunctive paroxetine or bupropion as compared with optimised mood stabiliser or antipsychotic treatment [8]. The second, the EMBOLDEN-II study, compared the efficacy of quetiapine with placebo, including paroxetine as a comparator [9]. Although quetiapine was found to be superior to placebo for treating acute depressive episodes in bipolar I and II disorder, paroxetine was not.

Findings from meta-analyses regarding the efficacy of antidepressants have been conflicting. While one found no advantage of antidepressants over placebo [10], three others have suggested greater efficacy of antidepressants compared with placebo in acute bipolar depression [11–13]. In a double-blind comparison trial of venlafaxine versus lithium monotherapy, venlafaxine had significantly greater response and remission rates, without an increase in hypomanic symptoms in bipolar II depression [14]. A further follow-up study of bipolar II patients in remission from a depressive episode demonstrated a lower relapse rate for fluoxetine compared with lithium or placebo, again without an increase in hypomanic symptoms [15].

The frequency and severity of antidepressant-associated mood elevations are significantly higher in bipolar I patients compared with bipolar II [16]. A large naturalistic study found antidepressant monotherapy to be associated with an increased risk of mania in bipolar I patients, while in those also receiving a mood stabiliser, this higher risk was not seen [17]. The risk seems particularly increased with tricyclic-antidepressants (TCAs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine compared with selective serotonin reuptake inhibitors (SSRIs) [11, 18].

While there may be a role for the cautious use of antidepressant monotherapy in select bipolar II patients who have previously demonstrated a favourable response, monitoring closely for any adverse reactions such as hypomania or agitation, there is an overall consensus that, especially in bipolar I patients, antidepressants should only be prescribed in combination with antimanic or antipsychotic medications [7]. If an antidepressant is to be prescribed, an SSRI or buproprion is generally recomended, while TCAs are usually best avoided. [19].

Mood Stabilisers

Lithium

The use of lithium in treating bipolar depression is supported by a number of early small double-blind trials suggesting superiority of lithium compared with placebo; however, most of these studies had methodological shortcomings [20]. In the only modern, rigorously conducted RCT (EMBOLDEN I), although quetiapine demonstrated superiority over placebo in the treatment of acute bipolar depression, lithium monotherapy did not significantly differ from placebo in reducing depressive symptom scores [21]. It should be noted, in this trial, median serum lithium levels were at the lower end of target range (0.6 mEq/L) and 35% of patients had serum concentrations below this level. Indeed, higher serum levels may be required for sufficient antidepressant effects, but this comes with an increased risk of adverse reactions. Nonetheless, there is evidence that lithium prevents depressive relapse, albeit with more robust protective effects on manic relapse [22, 23], and has an important role in reducing suicide risk in bipolar disorder patients [24].

Lamotrigine

Initial findings from five trials investigating the efficacy of lamotrigine in acute bipolar I and II depression were essentially negative in regard to the primary outcome [25]; however, a subsequent meta-analysis, which pooled data from these trials, determined a modest beneficial effect of lamotrigine on depressive symptoms [26]. Further analysis showed a more substantial effect in those patients with a baseline Hamilton Rating Scale for Depression (HAM-D) score of 24 and above, while in patients with scores below 24 at entry, the high placebo response likely prevented detection of an effect of lamotrigine in individual studies. Add-on studies have shown additional benefits of combining lamotrigine with lithium [27] and with quetiapine [28] treatment in bipolar depression.

Lamotrigine is approved by the FDA as a maintenance treatment in bipolar disorder with evidence for effectiveness in protecting against depressive and manic relapses with more robust effects against depression [29]. Although it may be used in acute bipolar depression, a practical consideration

which may limit clinical utility is the need for cautious dose titration to avoid potential dermatological complications.

Valproate

There are a limited number of small studies of valproate in bipolar depression which have been summarised in two meta-analyses [30, 31]. Taken together, these provide some evidence to support efficacy of valproate monotherapy in bipolar depression although a larger study would be helpful if it confirmed these putative acute benefits. There is also limited evidence to suggest that valproate protects against depressive relapse when used as a maintenance treatment [32], but again this is based on a small number of participants. The BALANCE trial compared valproate, lithium and their combination in a randomised open-label relapse prevention trial [23]. Trial findings demonstrated lithium monotherapy and lithium in combination with valproate were superior to valproate alone in preventing both manic and depressive relapses. Naturally, patients and clinicians need to consider acceptability and potential side-effect burden when deciding between lithium, valproate or their combination as longer term treatments in bipolar disorder.

Carbamazepine

The evidence base concerning the treatment of bipolar depression with carbamazepine is poor. A few early trials exist; however, most are uncontrolled and open label with small numbers of subjects. In one RCT comparing treatment with placebo versus carbamazepine for 12 weeks, although carbamazepine failed to significantly differentiate from placebo in depressive symptom measures at most post-baseline measure points, there was a higher clinical response rate at endpoint compared with placebo (30/47 = 63.8% vs. 8/23 = 34.8%, $p = 0.044$) [33]. In a Cochrane review of oxcarbazepine, a keto derivative of carbamazepine, as an adjunctive to lithium, oxcarbazepine reduced depression rating scale scores more than carbamazepine in a group of manic participants [34]. However, the role of this agent in bipolar depression remains poorly investigated.

Antipsychotics

Several second-generation antipsychotic medications have demonstrated effectiveness in treating bipolar depression. However, efficacy cannot be supported for the class as a whole with evidence instead suggesting a role for specific agents. Notably, these include quetiapine, olanzapine, lurasidone and most recently cariprazine.

Quetiapine

A number of trials have found quetiapine to be effective both as a short-term treatment and for relapse prevention in bipolar depression. Two initial RCTs demonstrated acute effectiveness of quetiapine at doses of 300 mg and 600 mg in bipolar I and II depression as early as week one [35, 36]. In two subsequent RCTs exploring the efficacy and tolerability of quetiapine and active comparators lithium and paroxetine, quetiapine again outperformed placebo in attenuating depressive symptoms while the active comparators did not [9, 21]. Placebo-controlled studies of quetiapine extended release (XR) monotherapy have also consistently demonstrated efficacy in bipolar depression [37–39]. In terms of relapse prevention, in patients with bipolar I disorder previously stabilised on quetiapine, continued maintenance therapy with quetiapine significantly increases time to recurrence of depressive or manic relapse compared with placebo [40], regardless of any combination with lithium or valproate [41]. Although effective in bipolar depression, quetiapine may not always be tolerated, particularly with regard to adverse effects including excess sedation, somnolence and weight gain [42].

Olanzapine ± Fluoxetine

Olanzapine monotherapy has shown superior benefits to placebo in the treatment of bipolar depression with a modest antidepressant effect [43–45]. In a subpopulation analysis of Japanese patients, there was a greater benefit on bipolar depression scores [46]. There is additional evidence to support a prophylactic effect as olanzapine delays relapse into subsequent mood episodes compared with placebo in bipolar disorder patients who have already responded to olanzapine for a manic or mixed episode [47].

In the original RCT, the combination of olanzapine with fluoxetine separated further from placebo than olanzapine monotherapy [43] and the efficacy of this combination has been further supported by findings from comparison studies [48–50]. Compared with lamotrigine, in patients with bipolar I depression, those receiving olanzapine + fluoxetine had significantly greater improvement in depressive symptoms at week 7 and week 25 time points [48, 50]. However, olanzapine + fluoxetine treatment was associated with significantly greater rates of side effects including somnolence, increased appetite, dry mouth, sedation, weight gain and tremor. Additionally, in olanzapine + fluoxetine-treated patients, weight, total cholesterol and triglyceride levels were all significantly elevated compared with those treated with lamotrigine. This suggests that although olanzapine + fluoxetine may be more effective in bipolar depression; lamotrigine shows better tolerability.

Lurasidone

Evidence to support efficacy of lurasidone in the treatment of bipolar depression comes from three large placebo-controlled studies [51–53]. In the first, comparing lurasidone monotherapy versus placebo in bipolar I depression over a 6-week period, lurasidone significantly reduced depressive symptoms compared with placebo [51]. Two further placebo-controlled trials showed significant benefits of lurasidone when used as an adjunct to lithium or valproate in improving depressive symptoms in bipolar depression [52, 53]. It is worth mentioning a final RCT of lurasidone in major depressive disorder with subthreshold hypomanic symptoms (mixed features) showed that lurasidone was also effective in reducing depressive symptoms and overall illness severity in this patient group [54].

Overall, lurasidone seems better tolerated than other antipsychotic medications but notable adverse events include akathisia, somnolence, extrapyramidal symptoms and nausea. Importantly lurasidone produces minimal changes in weight, lipids and measures of glycaemic control [51–53]. When balancing benefits and harms of potential treatment options, although lurasidone may not be quite as efficacious as quetiapine or olanzapine + fluoxetine, it would appear to demonstrate an enhanced tolerability profile, increasing its overall utility [55].

Cariprazine

Cariprazine is a novel antipsychotic that is a selective dopamine D_3 and D_2 partial agonist with higher affinity for the D_3 versus D_2 receptor [56]. An initial 8-week phase IIB study of cariprazine at a dose of 1.5 mg/day demonstrated consistent efficacy compared with placebo in bipolar I depression and was generally well tolerated [57]. A larger phase III study demonstrated that cariprazine at both 1.5 mg/day and 3.0 mg/day was significantly more effective than placebo in improving depressive symptoms in bipolar I depression [58•]. Common adverse events in participants receiving cariprazine were nausea, akathisia, dizziness and sedation while mean changes in weight and metabolic parameters were relatively small and comparable across treatment groups. The use of cariprazine in the treatment of depressive episodes associated with bipolar I disorder has since been approved by the FDA.

Others (Aripiprazole and Ziprasidone)

There is limited evidence from open-label studies to suggest benefits of aripiprazole in bipolar depression as an add-on treatment [59, 60]. However, in two identically designed, 8-week, RCTs of aripiprazole monotherapy in bipolar depression, although significant differences in depressive symptoms were seen during weeks 1–6, aripiprazole did not significantly separate from placebo at week 8 (the primary end point) [61].

Similar to aripiprazole, there are two negative RCTs of ziprasidone in the treatment of bipolar depression [62]. Furthermore, in another large study examining efficacy of adjunctive ziprasidone to pre-existing mood stabiliser in acute bipolar depression, adjunctive ziprasidone treatment failed to separate from mood stabiliser alone in depression ratings at 6 weeks [63].

Taken together, these findings suggest aripiprazole and ziprasidone monotherapy are probably not effective in bipolar depression and should not be used routinely [64].

Alternative and Experimental Treatments

Pramipexole

With study findings supporting efficacy of cariprazine in bipolar depression, dopamine agonism/partial agonism has been suggested as a potential mechanism for antidepressant action [65•]. Pramipexole is a dopamine D2/D3 agonist commonly used in the management of Parkinson's disease. There have been two small RCTs of pramipexole combined with existing mood stabiliser treatment both suggesting efficacy and tolerability in bipolar depression [66, 67]. Neither study detected an increased risk of switching to mania/hypomania in the pramipexole-treated groups; however, these are small studies and the data are not sufficient to exclude this potential risk.

Modafinil and Armodafinil

The wakefulness-promoting agent modafinil and its longer lasting R-enantiomer (armodafinil) both act to inhibit dopamine-reuptake and have a potential adjunctive role in bipolar depression [68]. One placebo-controlled trial examining adjunctive modafinil at doses of 100 mg–200 mg/day in bipolar depression found significantly greater improvement in depressive symptoms in the modafinil group at week 2, maintained through to week 6 [69]. A phase II and subsequent phase III study of adjunctive armodafinil 150 mg/day in bipolar I depression again demonstrated significantly improved depressive symptoms compared with placebo and was generally well tolerated [70, 71]. However, in two further double-blind RCTs of adjunctive armodafinil in bipolar I depression, although armodafinil reduced depressive symptoms to a greater extent than placebo, it did not separate from placebo in the primary efficacy outcomes in either study [72, 73]. A recent meta-analysis combining these studies found that compared with placebo, augmentation with modafinil or armodafinil was associated with significantly greater treatment response and remission, encouraging further studies that delineate subtypes of bipolar depression responsive to these novel dopamine enhancing agents [68].

Ketamine

There is growing interest in the potential of ketamine, an uncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, for the treatment of unipolar and bipolar depression. Rapid reductions in depressive symptoms have been reliably demonstrated following a single subanaesthetic ketamine infusion, including in cases of treatment-resistance [74]. Although not fully understood, ketamine's mechanism of antidepressant action is thought to be mediated through NMDA receptor antagonism, resulting in increased cortical glutamate, increased α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) signalling and downstream effects on synaptogenic and neuroplastic pathways. [75].

In a randomised, placebo-controlled, double-blind, crossover add-on study of 18 patients with treatment-resistant bipolar depression already receiving lithium or valproate, following a single ketamine infusion (0.5 mg/kg over 40 min) depressive symptoms significantly improved within 40 min compared with placebo and remained significant through day 3 [76]. There was an impressive response rate with 71% of subjects showing a response to ketamine compared with only 6% for placebo. These findings have been replicated in a similarly designed study of 15 patients with treatment-resistant bipolar depression (maintained on lithium or valproate), which demonstrated a comparable rapid and robust antidepressant response following a single ketamine infusion, alongside a significant improvement in suicidal ideation [77]. The most common side effect was acute dissociative symptoms; otherwise, ketamine was generally well tolerated.

Although ketamine may offer a rapid antidepressant effect in cases of bipolar depression, unfortunately the effect is not sustained in the long term. While one option is repeated ketamine infusions [78], the feasibility, accessibility and resources required can limit availability and other routes of administration (oral, sublingual, intranasal, intramuscular, subcutaneous) could prove preferred alternatives for repeat administrations [79]. However, comparatively fewer studies have fully evaluated these alternative routes and further investigation is warranted.

An intranasal formulation of ketamine's (S)-enantiomer, esketamine, was recently approved by the FDA for unipolar depression. Although no trials have specifically examined the use of this formulation in bipolar depression, it could be a potential avenue to consider and explore in the future.

Memantine

Memantine is a non-competitive NMDA antagonist that lacks dissociative side effects associated with ketamine at therapeutic doses and has also been investigated as an adjunctive treatment in bipolar depression. Although results of one RCT suggested an early antidepressant effect of memantine augmentation to lamotrigine in bipolar depression, this effect failed to separate from placebo at the 8-week trial endpoint [80]. In an RCT examining effects of memantine augmentation to valproate in bipolar II depression, tumour necrosis factor α levels (TNF-α) were significantly lower in the memantine group, suggesting an anti-inflammatory effect, but there was no significant advantage over placebo in terms of antidepressant effect [81]. A meta-analysis of these trials showed no significant benefit of memantine over placebo augmentation in bipolar depression but advised there was not enough evidence to draw meaningful conclusions [82].

Thyroxine/Levothyroxine

Thyroid abnormalities associated with bipolar disorder are a significant problem that can lead to poor outcomes if not recognised and treated [83]. The benefits of adjunctive treatment with thyroid hormones at supraphysiologic doses have been explored bipolar depression. In a placebo-controlled study, the addition of levothyroxine to continuing treatment with mood stabiliser and/or antidepressant medication in bipolar depression showed no significant benefit over placebo [84]. Interestingly, a secondary analysis revealed a significant difference in female patients only. More recently a double-blind, placebo-controlled trial in 32 patients with treatment-resistant rapid cycling bipolar disorder found that following adjunctive levothyroxine treatment patients spent significantly less time depressed or in a mixed state and greater time euthymic (*within groups*) [85]. *Between groups*, those in the levothyroxine group had a significantly greater increase in time euthymic and decrease in time in the mixed state compared with the placebo group.

Omega-3 Fatty Acids

There is limited evidence for the use of omega-3 fatty acids in bipolar depression and findings of individual studies have not been consistent. While one RCT examining the efficacy of adjunctive ethyl-eicosapentaenoic acid (EPA) in bipolar depression (1–2 g/day) found a significant improvement in HAM-D scores compared with placebo [86], another RCT found no significant difference between adjunctive EPA (6 g/day) and placebo in changes from baseline depressive symptoms [87]. A later meta-analysis, of 5 pooled datasets ($n = 291$), revealed a significant effect in favour of adjunctive omega-3 on the outcome of bipolar depression with a moderate effect size but uncertainty remains regarding optimum formulation and dosage [88].

Mifepristone

At high doses, the progesterone receptor antagonist mifepristone is an antagonist of the glucocorticoid receptor (GR)

subtype of corticosteroid receptor and preliminary evidence demonstrated potential cognitive-enhancing and mood-elevating properties in bipolar disorder [89]. However, in a larger RCT examining adjunctive mifepristone (600 mg/day) for 1 week in 60 patients with bipolar depression, although treatment was well tolerated and a beneficial effect in spatial working memory was demonstrated, there was no significant effect of mifepristone on depressive symptoms [90]. The lack of antidepressant effect may have been dose related as the dose used would not be expected to reliably generate plasma levels within a therapeutic range suggested by previous work in psychotic depression [91].

Non-pharmacological

Although there are limited RCTs of electroconvulsive therapy (ECT) in mania and bipolar depression, there is a wide consensus that ECT is an effective treatment for both acute mania and bipolar depression even in pharmacotherapy-resistant patients [92]. In large sample of drug-resistant bipolar depressed patients, at the end of an ECT course, an antidepressant response was seen in 201 out of 295 individuals (68.1%) [93] and another trial suggests ECT may be more effective than pharmacological treatment in treatment-resistant bipolar depression [94].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation therapy. There is growing evidence to support its use in bipolar depression with findings from a meta-analysis suggesting rTMS to be a safe, effective treatment option and does not appear to be associated with treatment-emergent affective switches [95]. Efforts to develop the technique are ongoing with encouraging results in bipolar depression using a novel approach called 'deep' TMS or (dTMS) to stimulate deeper brain regions [96].

Other non-invasive physical treatments focussing on sleep disturbances and circadian rhythm dysfunction including sleep deprivation, sleep phase advance and light therapy may serve as potential add-on treatment options in bipolar depression to accelerate and sustain antidepressant response [97, 98].

Last, but by no means least, adjunctive psychotherapy has an important role in terms of relapse prevention and episode stabilisation in bipolar disorder [99]. Psychotherapy is an opportunity for psychoeducation and may help to identify and monitor early signs of mood change, develop strategies for relapse prevention, explore and manage relationship between mood, stress and interpersonal difficulties, encourage medication adherence, establish regular sleep-wake cycles and address substance misuse [100]. Although a discussion of different psychotherapy modalities is beyond the scope of this review, in terms of bipolar depression, cognitive behavioural therapy (CBT), family therapy and psychoeducation may be particularly useful in protecting against recurrences [99, 100].

Summary and Future Perspectives

A summary of established and alternative/experimental pharmacological treatments in bipolar depression discussed in this review is provided in Table 1. The development of guidance and expert treatment recommendations for bipolar depression has been largely informed by the strength of evidence for particular drugs or by direct comparative data [19]. However, as shown in Table 2, treatment recommendations are not always consistent, with large variation observed in terms of guideline recommendations and interpretation of available evidence. As one example, the 2017 International College of Neuro-Psychopharmacology (CINP) treatment guidelines recommend aripiprazole and imipramine monotherapy as third-line strategies in bipolar depression [102•]. Uncertainty remains with regard to the relative efficacy and safety of antidepressants, mood stabilisers, antipsychotics and experimental treatments for bipolar depression.

One attempt to address this issue has come from multiple-treatment meta-analyses. In a large network meta-analysis of 29 studies including 8331 subjects, olanzapine + fluoxetine, lurasidone, olanzapine, valproate, SSRIs and quetiapine ranked highest for effect size and olanzapine + fluoxetine also ranked highest for response [64]. A further meta-analysis of 24 trials (7307 subjects) in bipolar depression found statistical superiority over placebo for olanzapine + fluoxetine ≥ valproate > quetiapine >lurasidone > olanzapine > aripiprazole and carbamazepine (in order of effect size) [104]. However, these meta-analyses are limited by the small numbers of controlled trials of bipolar depression treatments and by the methods used to assess efficacy meaning certain studies cannot be included as parameters such as outcome and trial duration do not match and cannot be reliably compared with others. This is particularly relevant for early studies of lithium. Furthermore, these network meta-analyses may not be stable as rankings are influenced by inclusion criteria and indirect comparisons sometimes contradict direct comparison findings [65•].

Mindful of these limitations and considering the available evidence, quetiapine is likely the most efficacious established treatment for bipolar depression. Other first-line agents to consider include lurasidone, olanzapine ± fluoxetine, lamotrigine and valproate. Cariprazine may become more widely used in the future. Lithium is also probably effective in bipolar depression, but the supporting evidence is limited. Alternative treatments including pramipexole, modafinil/armodafinil, omega-3 fatty acids and thyroxine can be used to augment the treatment of bipolar depression. In cases of treatment-resistance, ketamine may provide rapid reductions in depressive symptoms, but challenges remain in considering the most appropriate route of administration and how best to maintain response. Although still highly stigmatised, ECT is another effective treatment and should also be considered in cases of treatment-resistance and high suicidal risk.

Table 1 Summary of established and alternative/experimental pharmacological treatments in bipolar depression

Drug/combination	Summary	Placebo-controlled trials (number in efficacy analysis)	Efficacy	Refs
Established treatments:				
Quetiapine	- Five large RCTs have demonstrated clear efficacy for quetiapine monotherapy at 300 mg and 600 mg/day in bipolar I and bipolar II depression. - Two subsequent RCTs in Chinese and Japanese patients demonstrated further efficacy of quetiapine extended release (XR) 300 mg/day in bipolar I and II depression.	7 (3112)	+ + +	[9, 21, 35–39]
Lurasidone	- One large RCT showing good effect of lurasidone as monotherapy in bipolar I depression. - Two further RCTs showed significant benefit of lurasidone as an adjunct to mood stabilisers compared with placebo in bipolar I depression.	Monotherapy: 1 (485) Adjunct: 2 (682)	+ + +	[51–53]
Olanzapine	- Two large RCTs showing Olanzapine monotherapy is effective in bipolar I depression. - Another small RCT from China demonstrating significantly greater improvements in depressive symptoms relative to placebo.	3 (1282)	+ +	[43–45]
Olanzapine ± fluoxetine	- The combination of olanzapine with fluoxetine separated further from placebo than olanzapine monotherapy in the only placebo-controlled trial. - A double-blind comparison study and 6-month follow-up suggests olanzapine + fluoxetine may be more effective than lamotrigine in bipolar I depression.	1 (437)	+ + +	[43] [48, 50]
Cariprazine	- In the first RCT which compared cariprazine 0.75 mg/day, 1.5 mg/day and 3.0 mg/day found cariprazine 1.5 mg/day demonstrated consistent efficacy compared with placebo in bipolar I depression. - Subsequent phase III RCT found cariprazine at both 1.5 mg/day and 3.0 mg/day was significantly more effective than placebo in improving depressive symptoms in bipolar I depression.	2 (1045)	+ +	[57, 58•]
Lamotrigine	- Modest beneficial effect of lamotrigine in bipolar I and II depression determined from meta-analysis, however numerous failed individual trials. - Effective in protecting against depressive relapses in bipolar disorder. - Cautious dose titration required to avoid potential dermatological complications.	5 (1071)	+ +	[25, 26] [29]
Valproate	- Four small RCTs of valproate in bipolar depression summarised in meta-analyses which support antidepressant efficacy. - Limited evidence suggests valproate protects against depressive relapse when used as a maintenance treatment.	4 (140)	+ +	[30, 31] [32]
Lithium	- Lithium is likely effective in treating bipolar depression but supporting data has methodological shortcomings. Only one modern rigorously conducted RCT. - Evidence that lithium prevents depressive relapse, however more robust protective effects on manic relapse. - Important role in reducing suicide risk in bipolar disorder.	1 (265)	+ / + +	[21] [22–24]
Carbamazepine	- In one small RCT, carbamazepine did not significantly differentiate from placebo in measures of depressive symptoms at most post-baseline time points. However, there was a higher clinical response rate at endpoint compared with placebo.	1 (70)	+	[33]
Alternative/experimental treatments:				
Pramipexole	- Two small placebo-controlled trials, one in bipolar I and another in bipolar II depression, suggest efficacy in bipolar depression when used as adjunct to existing mood stabiliser treatment.	Adjunct: 2 (43)	+ +	[66, 67]
Modafinil/armodafinil	- One positive RCT of modafinil 100–200 mg/day when used as an adjunct treatment in bipolar depression. - Four RCTs of adjunctive armodafinil in bipolar I depression of which two showed a significant benefit over placebo, while in the remaining two, armodafinil did not separate from placebo in primary efficacy outcomes. - Findings combined in recent meta-analysis that suggests augmentation with modafinil or armodafinil is associated with significantly greater treatment response and remission in bipolar depression.	Adjunct: 5 (1587)	+ +	[69–73] [68]
Ketamine (IV)	- Two randomised, placebo-controlled, double-blind, crossover trials in treatment-resistant bipolar I and II depressed patients. - High response rate (~ 70%) to single ketamine infusion 0.5 mg/kg over 40 mins in both trials. - Antidepressant effects not long-lasting for most patients. - Most common side-effect was acute dissociative symptoms.	Adjunct: 2 (33) (Crossover trials-subjects received ketamine and placebo)	+ +	[75, 76]
Memantine	- One small and one larger RCT failed to show a significant advantage of memantine augmentation (lamotrigine and valproate respectively) over placebo in terms of antidepressant effect in bipolar depression.	Adjunct: 2 (261)	–	[80, 81]

Table 1 (continued)

Drug/combination	Summary	Placebo-controlled trials (number in efficacy analysis)	Efficacy	Refs
Thyroxine/levothyroxine	- One RCT found no significant benefit of adjunct levothyroxine over placebo in bipolar depression. - Another RCT in treatment-resistant rapid cycling bipolar disorder comparing adjunctive levothyroxine ($L\text{-}T_4$), triiodothyronine (T_3) and placebo found *within groups*, post-treatment the $L\text{-}T_4$ group spent significantly less time in depressed or in a mixed state and greater time euthymic. *Between groups*, the L-T4 group had a significantly greater increase in time euthymic and decrease in time in the mixed state than the placebo group.	Adjunct: 2 (94)	+	[84, 85]
Omega-3 fatty acids	- Meta-analysis of five RCTs of omega-3 in bipolar I and II depression found a significant effect in favour of omega-3 over placebo with moderate effect size.	Adjunct: 5 (291)	+ +	[88]
Mifepristone	-Preliminary evidence suggested potential cognitive-enhancing and mood-elevating properties in bipolar disorder. - Larger RCT examining adjunctive mifepristone 600 mg/day in bipolar depression failed to demonstrate significant improvement in depressed mood. Mifepristone treatment was associated with improvement in cognitive function (spatial working memory).	Adjunct: 1 (60)	-/+	[89] [90]

The rapid improvement in depressive symptoms occurring with ketamine administration, taking place within hours to days rather than weeks to months, represents a paradigm shift in the treatment of depression and now the ultimate goal is the development of rapid acting treatment strategies with a prolonged antidepressant response. An intranasal formulation of the (S)-enantiomer, esketamine, has been developed with promising results following repeated administration in treatment-resistant unipolar depression [105]. Although there have been no trials of intranasal esketamine in bipolar depression completed to date, work is now underway to determine safety and efficacy of an inhaled esketamine formulation in bipolar depression (ClinicalTrials.gov ID: NCT03965871). Alternative and better tolerated ketamine-like agents that affect glutamate neurotransmission may offer future promise in both unipolar and bipolar depression [106, 107]. The psychedelic drug psilocybin, a $5\text{-}HT_{2A}$ partial agonist, is another compound with novel antidepressant mechanisms, currently being investigated in unipolar major depressive disorder (ClinicalTrials.gov ID: NCT03775200, NCT03866174). While this may not be a suitable option to explore in bipolar I depression, due to the potential risk of mania, it may be an interesting avenue to explore in the future in carefully selected bipolar II depressed individuals.

Other novel treatment strategies under investigation in bipolar depression include adjunctive anti-inflammatory agents and probiotics. Several proof-of-concept trials have shown encouraging results for anti-inflammatory agents in the treatment of bipolar depression with moderate effect sizes and good tolerability [101, 103•, 108•]. Results from trials of probiotics in bipolar depression are awaited (ClinicalTrials.gov IDs: NCT02155972, NCT03349528). Ideally large future studies, using stratified samples enriched with individuals with immune dysfunction or microbiome abnormalities, will establish the role of adjunctive anti-inflammatory agents and probiotics in bipolar depression.

Conclusions

When deciding treatment options in bipolar depression, it is important to balance to potential benefits and harms. The treatments discussed in this review have substantial differences in terms of adverse effect profile, tolerability and acceptability. Considering each case individually and involving the patient in their treatment planning are key.

Despite the severe clinical and socioeconomic impact, research into the treatment of bipolar depression remains limited. Further work using consistent, optimal trial designs as well as further investigation into novel compounds and treatment interventions is warranted.

Table 2 Selected recent guidelines and treatment recommendations for bipolar depression (within last 5 years)

Guideline	Summary of recommendations
National Institute of Clinical Excellence (NICE) 2014 [101]	- First line: olanzapine + fluoxetine or quetiapine - Second line: olanzapine or lamotrigine - If develops depression and already taking lithium: - Check plasma levels and increase dose if inadequate - Add olanzapine + fluoxetine or quetiapine first line or lamotrigine second line - If develops depression and already taking valproate: - Check plasma levels and increase dose if inadequate - Add olanzapine + fluoxetine or quetiapine first line or lamotrigine second line - Additional psychological interventions: cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy * Always consider person's preference and previous response to treatment
British Association for Psychopharmacology 2016 [65•]	- Patients not already taking long-term treatment: Consider (a) quetiapine; (b) lurasidone; (c) olanzapine - Lamotrigine plus mood stabiliser or antipsychotic preventing recurrence of mania - If considering antidepressant treatment, co-prescribe with antimanic or antipsychotic, especially in individuals with a history of mania. Olanzapine + fluoxetine has support as a specific treatment combination - If depressive symptoms are less severe, lithium may be considered - Consider ECT in cases of treatment resistance, high risk of suicide, psychosis, not eating or drinking because of depression or severe depression during pregnancy - Additional psychological interventions: cognitive behaviour therapy, family-focused therapy or interpersonal rhythm therapy
International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults 2017 [102•]	- First step: quetiapine or lurasidone. Depending on patient preference and availability, consider cognitive behaviour therapy in addition to medication - Second step: (a) olanzapine ± fluoxetine; (b) mood stabiliser plus lurasidone, modafinil or pramipexole; (c) lithium plus lamotrigine; (d) add escitalopram or fluoxetine to existing treatment - Third step: (a) valproate, aripiprazole, imipramine, phenelzine, carbamazepine or lamotrigine monotherapy; (b) lithium plus L-sulpiride - Fourth step: (a) tranylcypromine or lithium monotherapy; (b) venlafaxine plus antimanic; (c) armodafinil or IV ketamine with mood stabiliser; (d) lithium plus fluoxetine or lamotrigine; (e) mood stabiliser plus levothyroxine (L-T4); (f) lithium plus oxcarbazepine - Fifth step: ECT or various medication combinations depending on prescriber's knowledge or personal experience
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder [103•]	- First-line: (a) quetiapine; (b) lurasidone plus lithium or valproate; (c) lithium; (d) lamotrigine; (e) lurasidone; (e) lamotrigine (adj) - Second-line: (a) valproate; (b) SSRIs/bupropion plus antimanic or antipsychotic; (c) ECT; (d) cariprazine; (e) olanzapine + fluoxetine -Third-line: (*In alphabetical order*) (a) aripiprazole (adj); (b) armodafinil (adj); (c) asenapine (adj); (d) carbamazepine; (e) eicosapentaenoic acid (EPA) (adj); (f) ketamine (IV) (adj); (g) light therapy ± total sleep deprivation (adj); (h) levothyroxine (adj); (i) modafinil (adj); (j) N-acetylcysteine (adj); (k) olanzapine; (l) pramipexole (adj); (m) repetitive transmagnetic stimulation (rTMS) (adj); (n) SNRI/MAOI (adj)

This is a summary of each guideline's treatment recommendations, condensed for the purpose of the review. Please refer to individual guidelines for detailed recommendations and further analysis of supporting evidence. *ECT*, electroconvulsive therapy; *adj*, adjunctive; *SSRIs*, selective serotonin reuptake inhibitors; *SNRI*, serotonin and norepinephrine reuptake inhibitor; *MAOI*, monoamine oxidase inhibitor

Together this will widen the evidence-based treatment armamentarium in bipolar depression and allow more reliable treatment comparisons to be determined.

Funding Information This report represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards and international/national/institutional guidelines).

Conflict of Interest Luke A Jelen declares no potential conflicts of interest with respect to the research, authorship and/or publication of this article. Allan H Young reports personal fees from Lundbeck, grants from Janssen, personal fees from Janssen, grants from Livanova, personal fees from Livanova, grants from COMPASS, grants from COMPASS, personal fees from Sumitomo Dainippon Pharma, outside the submitted work; employment by King's College London; Honorary Consultant SLaM (NHS UK); paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma; consultant to Johnson & Johnson; consultant to Livanova; honoraria for attending advisory boards and presenting talks at meetings organised by LivaNova; principal Investigator in the Restore-Life VNS registry study funded by LivaNova; principal Investigator on ESKETINTRD3004: 'An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression;' principal Investigator on 'The Effects of Psilocybin on Cognitive Function in Healthy Participants;' principal Investigator on 'The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD);' grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK); no shareholdings in pharmaceutical companies.

Disclaimer The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Kupka RW, Altshuler LL, Nolen WA, Suppes T, Luckenbaugh DA, Leverich GS, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord. 2007;9(5):531–5. https://doi.org/10.1111/j.1399-5618.2007.00467.x.
2. Tondo L, Lepri B, Baldessarini RJ. Suicidal risks among 2826 Sardinian major affective disorder patients. Acta Psychiatr Scand. 2007;116(6):419–28. https://doi.org/10.1111/j.1600-0447.2007.01066.x.
3. Bonnin CM, Martinez-Aran A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, et al. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J Affect Disord. 2010;121(1–2):156–60. https://doi.org/10.1016/j.jad.2009.05.014.
4. Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. Acta Psychiatr Scand. 2008;118(5):337–46. https://doi.org/10.1111/j.1600-0447.2008.01237.x.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders 5. Washington, DC: American Psychiatric Association; 2013.
6. Swartz HA, Thase ME. Pharmacotherapy for the treatment of acute bipolar II depression: current evidence. J Clin Psychiatry. 2011;72(3):356–66. https://doi.org/10.4088/JCP.09r05192gre.
7. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry. 2013;170(11):1249–62. https://doi.org/10.1176/appi.ajp.2013.13020185.
8. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007;356(17):1711–22. https://doi.org/10.1056/NEJMoa064135.
9. McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry. 2010;71(2):163–74. https://doi.org/10.4088/JCP.08m04942gre.
10. Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry. 2011;72(2):156–67. https://doi.org/10.4088/JCP.09r05385gre.
11. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry. 2004;161(9):1537–47. https://doi.org/10.1176/appi.ajp.161.9.1537.
12. Vazquez GH, Tondo L, Undurraga J, Baldessarini RJ. Overview of antidepressant treatment of bipolar depression. Int J Neuropsychopharmacol. 2013;16(7):1673–85. https://doi.org/10.1017/S1461145713000023.
13. McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138–46. https://doi.org/10.1016/S2215-0366(16)30264-4.

14. Amsterdam JD, Lorenzo-Luaces L, Soeller I, Li SQ, Mao JJ, DeRubeis RJ. Short-term venlafaxine v. lithium monotherapy for bipolar type II major depressive episodes: effectiveness and mood conversion rate. Br J Psychiatry. 2016;208(4):359–65. https://doi.org/10.1192/bjp.bp.115.169375.
15. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am J Psychiatry. 2010;167(7):792–800. https://doi.org/10.1176/appi.ajp.2009.09020284.
16. Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry. 2008;69(10):1589–601. https://doi.org/10.4088/jcp.v69n1009.
17. Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PK, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry. 2014;171(10):1067–73. https://doi.org/10.1176/appi.ajp.2014.13111501.
18. Tondo L, Vazquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010;121(6):404–14. https://doi.org/10.1111/j.1600-0447.2009.01514.x.
19. Taylor DM, Barnes TRE, Young AH. The Maudsley prescribing guidelines in psychiatry. Thirteenth Edition ed: John Wiley & Sons Ltd.; 2018.
20. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry. 2010;11(2):81–109. https://doi.org/10.3109/15622970903555881.
21. Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry. 2010;71(2):150–62. https://doi.org/10.4088/JCP.08m04995gre.
22. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord. 2014;2:15. https://doi.org/10.1186/s40345-014-0015-8.
23. Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010;375(9712):385–95. https://doi.org/10.1016/S0140-6736(09)61828-6.
24. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 2013;346:f3646. https://doi.org/10.1136/bmj.f3646.
25. Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disord. 2008;10(2):323–33. https://doi.org/10.1111/j.1399-5618.2007.00500.x.
26. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry. 2009;194(1):4–9. https://doi.org/10.1192/bjp.bp.107.048504.
27. van der Loos ML, Mulder PG, Hartong EG, Blom MB, Vergouwen AC, de Keyzer HJ, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(2):223–31. https://doi.org/10.4088/jcp.08m04152.
28. Geddes JR, Gardiner A, Rendell J, Voysey M, Tunbridge E, Hinds C, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 x 2 factorial randomised trial. Lancet Psychiatry. 2016;3(1):31–9. https://doi.org/10.1016/S2215-0366(15)00450-2.
29. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry. 2004;65(3):432–41. https://doi.org/10.4088/jcp.v65n0321.
30. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. J Affect Disord. 2010;124(3):228–34. https://doi.org/10.1016/j.jad.2009.11.008.
31. Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, et al. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord. 2010;122(1–2):1–9. https://doi.org/10.1016/j.jad.2009.10.033.
32. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev. 2013;10:CD003196. https://doi.org/10.1002/14651858.CD003196.pub2.
33. Zhang ZJ, Kang WH, Tan QR, Li Q, Gao CG, Zhang FG, et al. Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. J Psychiatr Res. 2007;41(3–4):360–9. https://doi.org/10.1016/j.jpsychires.2005.06.002.
34. Vasudev A, Macritchie K, Vasudev K, Watson S, Geddes J, Young AH. Oxcarbazepine for acute affective episodes in bipolar disorder. Cochrane Database Syst Rev. 2011;12:CD004857. https://doi.org/10.1002/14651858.CD004857.pub2.
35. Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. 2005;162(7):1351–60. https://doi.org/10.1176/appi.ajp.162.7.1351.
36. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol. 2006;26(6):600–9. https://doi.org/10.1097/01.jcp.0000248603.76231.b7.
37. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J Affect Disord. 2010;121(1–2):106–15. https://doi.org/10.1016/j.jad.2009.10.007.
38. Li H, Gu N, Zhang H, Wang G, Tan Q, Yang F, et al. Efficacy and safety of quetiapine extended release monotherapy in bipolar depression: a multi-center, randomized, double-blind, placebo-controlled trial. Psychopharmacology. 2016;233(7):1289–97. https://doi.org/10.1007/s00213-016-4215-z.
39. Murasaki M, Koyama T, Kanba S, Takeuchi M, Shimizu Y, Arita E, et al. Multi-center, randomized, double-blind, placebo-controlled study of quetiapine extended-release formulation in Japanese patients with bipolar depression. Psychopharmacology. 2018;235(10):2859–69. https://doi.org/10.1007/s00213-018-4977-6.
40. Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B, Trial 144 Study I. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (trial 144: a randomized controlled study). J Clin Psychiatry.

2011;72(11):1452–1464. doi:https://doi.org/10.4088/JCP.11m06878.
41. Suppes T, Vieta E, Gustafsson U, Ekholm B. Maintenance treatment with quetiapine when combined with either lithium or divalproex in bipolar I disorder: analysis of two large randomized, placebo-controlled trials. Depress Anxiety. 2013;30(11):1089–98. https://doi.org/10.1002/da.22136.
42. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: a systematic review and meta-analysis. Drug Des Devel Ther. 2014;8:827–38. https://doi.org/10.2147/DDDT.S63779.
43. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry. 2003;60(11):1079–88. https://doi.org/10.1001/archpsyc.60.11.1079.
44. Wang M, Tong JH, Huang DS, Zhu G, Liang GM, Du H. Efficacy of olanzapine monotherapy for treatment of bipolar I depression: a randomized, double-blind, placebo controlled study. Psychopharmacology. 2014;231(14):2811–8. https://doi.org/10.1007/s00213-014-3453-1.
45. Tohen M, McDonnell DP, Case M, Kanba S, Ha K, Fang YR, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. Br J Psychiatry. 2012;201(5):376–82. https://doi.org/10.1192/bjp.bp.112.108357.
46. Katagiri H, Tohen M, McDonnell DP, Fujikoshi S, Case M, Kanba S, et al. Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Japanese subpopulation analysis of a randomized, double-blind, placebo-controlled study. BMC Psychiatry. 2013;13:138–10. https://doi.org/10.1186/1471-244X-13-138.
47. Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry. 2006;163(2):247–56. https://doi.org/10.1176/appi.ajp.163.2.247.
48. Brown EB, McElroy SL, Keck PE Jr, Deldar A, Adams DH, Tohen M, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry. 2006;67(7):1025–33. https://doi.org/10.4088/jcp.v67n0703.
49. Dube S, Tollefson GD, Thase ME, Briggs SD, Van Campen LE, Case M, et al. Onset of antidepressant effect of olanzapine and olanzapine/fluoxetine combination in bipolar depression. Bipolar Disord. 2007;9(6):618–27. https://doi.org/10.1111/j.1399-5618.2007.00491.x.
50. Brown E, Dunner DL, McElroy SL, Keck PE, Adams DH, Degenhardt E, et al. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. Int J Neuropsychopharmacol. 2009;12(6):773–82. https://doi.org/10.1017/S1461145708009735.
51. Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014;171(2):160–8. https://doi.org/10.1176/appi.ajp.2013.13070984.
52. Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014;171(2):169–77. https://doi.org/10.1176/appi.ajp.2013.13070985.
53. Suppes T, Kroger H, Pikalov A, Loebel A. Lurasidone adjunctive with lithium or valproate for bipolar depression: a placebo-controlled trial utilizing prospective and retrospective enrolment cohorts. J Psychiatr Res. 2016;78:86–93. https://doi.org/10.1016/j.jpsychires.2016.03.012.
54. Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, Pikalov A, Loebel A Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study Am J Psychiatry 2016;173(4):400–407. doi:https://doi.org/10.1176/appi.ajp.2015.15060770.
55. Ketter TA, Miller S, Dell'Osso B, Calabrese JR, Frye MA, Citrome L. Balancing benefits and harms of treatments for acute bipolar depression. J Affect Disord. 2014;169(Suppl 1):S24–33. https://doi.org/10.1016/S0165-0327(14)70006-0.
56. Campbell RH, Diduch M, Gardner KN, Thomas C. Review of cariprazine in management of psychiatric illness. Ment Health Clin. 2017;7(5):221–9. https://doi.org/10.9740/mhc.2017.09.221.
57. Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Nemeth G, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry. 2016;173(3):271–81. https://doi.org/10.1176/appi.ajp.2015.15020164.
58.• Earley W, Burgess MV, Rekeda L, Dickinson R, Szatmari B, Nemeth G, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. Am J Psychiatry. 2019;176(6):439–48. https://doi.org/10.1176/appi.ajp.2018.18070824 **This RCT demonstrated that the novel antipsychotic cariprazine, at both 1.5 mg/day and 3.0 mg/day, was effective, generally well tolerated and relatively safe in reducing depressive symptoms in adults with bipolar I depression.**
59. Ketter TA, Wang PW, Chandler RA, Culver JL, Alarcon AM. Adjunctive aripiprazole in treatment-resistant bipolar depression. Ann Clin Psychiatry. 2006;18(3):169–72. https://doi.org/10.1080/10401230600801176.
60. Mazza M, Squillacioti MR, Pecora RD, Janiri L, Bria P. Beneficial acute antidepressant effects of aripiprazole as an adjunctive treatment or monotherapy in bipolar patients unresponsive to mood stabilizers: results from a 16-week open-label trial. Expert Opin Pharmacother. 2008;9(18):3145–9. https://doi.org/10.1517/14656560802504490.
61. Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol. 2008;28(1):13–20. https://doi.org/10.1097/jcp.0b013e3181618eb4.
62. Lombardo I, Sachs G, Kolluri S, Kremer C, Yang R. Two 6-week, randomized, double-blind, placebo-controlled studies of ziprasidone in outpatients with bipolar I depression: did baseline characteristics impact trial outcome? J Clin Psychopharmacol. 2012;32(4):470–8. https://doi.org/10.1097/JCP.0b013e31825ccde5.
63. Sachs GS, Ice KS, Chappell PB, Schwartz JH, Gurtovaya O, Vanderburg DG, et al. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011;72(10):1413–22. https://doi.org/10.4088/JCP.09m05934.
64. Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. Acta Psychiatr Scand. 2014;130(6):452–69. https://doi.org/10.1111/acps.12343.
65.• Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30(6):495–553. https://doi.org/10.1177/0269881116636545 **Provides evidence-based guidelines for treating bipolar disorder and specifically bipolar depression. Recommendations are presented together with a more detailed review of the corresponding evidence, considering the strength of evidence and clinical implications.**

66. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry. 2004;161(3):564–6. https://doi.org/10.1176/appi.ajp.161.3.564.
67. Zarate CA Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol Psychiatry. 2004;56(1):54–60. https://doi.org/10.1016/j.biopsych.2004.03.013.
68. Nunez N, Singh B, Romo-Nava F, Joseph B, Veldic M, Cuellar-Barboza A, et al. Efficacy and tolerability of adjunctive modafinil /armodafinil in bipolar depression: a meta-analysis of randomized controlled trials. Bipolar Disord. 2019. https://doi.org/10.1111/bdi.12859.
69. Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, Walden J, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry. 2007;164(8):1242–9. https://doi.org/10.1176/appi.ajp.2007.06060981.
70. Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry. 2010;71(10):1363–70. https://doi.org/10.4088/JCP.09m05900gry.
71. Calabrese JR, Frye MA, Yang R, Ketter TA, Armodafinil Treatment Trial Study N. Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled, multicenter trial. J Clin Psychiatry. 2014;75(10):1054–61. https://doi.org/10.4088/JCP.13m08951.
72. Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder. J Affect Disord. 2015;181:87–91. https://doi.org/10.1016/j.jad.2015.04.012.
73. Frye MA, Amchin J, Bauer M, Adler C, Yang R, Ketter TA. Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. Int J Bipolar Disord. 2015;3(1):34. https://doi.org/10.1186/s40345-015-0034-0.
74. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol. 2015;30(3):152–63. https://doi.org/10.1002/hup.2475.
75. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010;67(8):793–802. https://doi.org/10.1001/archgenpsychiatry.2010.90.
76. Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 2012;71(11):939–46. https://doi.org/10.1016/j.biopsych.2011.12.010.
77. Lener MS, Niciu MJ, Ballard ED, Park M, Park LT, Nugent AC, et al. Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. Biol Psychiatry. 2017;81(10):886–97. https://doi.org/10.1016/j.biopsych.2016.05.005.
78. Zheng W, Zhou YL, Liu WJ, Wang CY, Zhan YN, Li HQ, et al. Rapid and longer-term antidepressant effects of repeated-dose intravenous ketamine for patients with unipolar and bipolar depression. J Psychiatr Res. 2018;106:61–8. https://doi.org/10.1016/j.jpsychires.2018.09.013.
79. Rosenblat JD, Carvalho AF, Li M, Lee Y, Subramanieapillai M, McIntyre RS. Oral ketamine for depression: a systematic review. J Clin Psychiatry. 2019;80(3). https://doi.org/10.4088/JCP.18r12475.
80. Anand A, Gunn AD, Barkay G, Karne HS, Nurnberger JI, Mathew SJ, et al. Early antidepressant effect of memantine during augmentation of lamotrigine inadequate response in bipolar depression: a double-blind, randomized, placebo-controlled trial. Bipolar Disord. 2012;14(1):64–70. https://doi.org/10.1111/j.1399-5618.2011.00971.x.
81. Lee SY, Chen SL, Chang YH, Chen PS, Huang SY, Tzeng NS, et al. The effects of add-on low-dose memantine on cytokine levels in bipolar II depression: a 12-week double-blind, randomized controlled trial. J Clin Psychopharmacol. 2014;34(3):337–43. https://doi.org/10.1097/JCP.0000000000000109.
82. McCloud TL, Caddy C, Jochim J, Rendell JM, Diamond PR, Shuttleworth C, et al. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. Cochrane Database Syst Rev. 2015;9:CD011611. https://doi.org/10.1002/14651858.CD011611.pub2.
83. Chakrabarti S. Thyroid functions and bipolar affective disorder. J Thyroid Res. 2011;2011:306367. https://doi.org/10.4061/2011/306367.
84. Stamm TJ, Lewitzka U, Sauer C, Pilhatsch M, Smolka MN, Koeberle U, et al. Supraphysiologic doses of levothyroxine as adjunctive therapy in bipolar depression: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2014;75(2):162–8. https://doi.org/10.4088/JCP.12m08305.
85. Walshaw PD, Gyulai L, Bauer M, Bauer MS, Calimlim B, Sugar CA, et al. Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: a double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3). Bipolar Disord. 2018;20(7):594–603. https://doi.org/10.1111/bdi.12657.
86. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry. 2006;188:46–50. https://doi.org/10.1192/bjp.188.1.46.
87. Keck PE Jr, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry. 2006;60(9):1020–2. https://doi.org/10.1016/j.biopsych.2006.03.056.
88. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012;73(1):81–6. https://doi.org/10.4088/JCP.10r06710.
89. Young AH, Gallagher P, Watson S, Del-Estal D, Owen BM, Ferrier IN. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. Neuropsychopharmacology. 2004;29(8):1538–45. https://doi.org/10.1038/sj.npp.1300471.
90. Watson S, Gallagher P, Porter RJ, Smith MS, Herron LJ, Bulmer S, et al. A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. Biol Psychiatry. 2012;72(11):943–9. https://doi.org/10.1016/j.biopsych.2012.05.029.
91. Blasey CM, Block TS, Belanoff JK, Roe RL. Efficacy and safety of mifepristone for the treatment of psychotic depression. J Clin Psychopharmacol. 2011;31(4):436–40. https://doi.org/10.1097/JCP.0b013e3182239191.
92. Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. J Affect Disord. 2011;132(1–2):1–13. https://doi.org/10.1016/j.jad.2010.08.017.
93. Perugi G, Medda P, Toni C, Mariani MG, Socci C, Mauri M. The role of electroconvulsive therapy (ECT) in bipolar disorder: effectiveness in 522 patients with bipolar depression, mixed-state,

mania and catatonic features. Curr Neuropharmacol. 2017;15(3):359–71. https://doi.org/10.2174/1570159X14666161017233642.

94. Schoeyen HK, Kessler U, Andreassen OA, Auestad BH, Bergsholm P, Malt UF, et al. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. Am J Psychiatry. 2015;172(1):41–51. https://doi.org/10.1176/appi.ajp.2014.13111517.
95. McGirr A, Karmani S, Arsappa R, Berlim MT, Thirthalli J, Muralidharan K, et al. Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. World Psychiatry. 2016;15(1):85–6. https://doi.org/10.1002/wps.20300.
96. Tavares DF, Myczkowski ML, Alberto RL, Valiengo L, Rios RM, Gordon P, et al. Treatment of bipolar depression with deep TMS: results from a double-blind, randomized, parallel group, sham-controlled clinical trial. Neuropsychopharmacology. 2017;42(13):2593–601. https://doi.org/10.1038/npp.2017.26.
97. Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biol Psychiatry. 2009;66(3):298–301. https://doi.org/10.1016/j.biopsych.2009.02.018.
98. Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspezia S, Pontiggia A, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. J Clin Psychiatry. 2005;66(12):1535–40. https://doi.org/10.4088/jcp.v66n1207.
99. Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. Am J Psychiatry. 2008;165(11):1408–19. https://doi.org/10.1176/appi.ajp.2008.08040488.
100. Swartz HA, Swanson J. Psychotherapy for bipolar disorder in adults: a review of the evidence. Focus (Am Psychiatr Publ). 2014;12(3):251–66. https://doi.org/10.1176/appi.focus.12.3.251.
101. Bipolar disorder: the NICE guideline on the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. National Institute for Health and Care Excellence: Clinical Guidelines. London2014.
102.• Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int J Neuropsychopharmacol. 2017;20(2):180–95. https://doi.org/10.1093/ijnp/pyw109 **Provides treatment guidelines for bipolar disorder in adults based on evidence-based data. There are separate recommendations for each of the major phases of bipolar disorder, including bipolar depression, expressed as a 5-step algorithm.**
103.• Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170. https://doi.org/10.1111/bdi.12609 **Evidence-based guidelines for the management of patients with bipolar disorder including specific recommendations for bipolar depression**.
104. Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry. 2014;47(2):43–52. https://doi.org/10.1055/s-0033-1363258.
105. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2018;75(2):139–48. https://doi.org/10.1001/jamapsychiatry.2017.3739.
106. Vazquez GH, Camino S, Tondo L, Baldessarini RJ. Potential novel treatments for bipolar depression: ketamine, fatty acids, anti-inflammatory agents, and probiotics. CNS Neurol Disord Drug Targets. 2017;16(8):858–69. https://doi.org/10.2174/1871527316666170728165648.
107. Jelen LA, King S, Stone JM. Alternatives to ketamine in depression: state-of-the-art and future perspectives. Ther Adv Psychopharmacol. 2018;8(3):95–8. https://doi.org/10.1177/2045125317749456.
108. Rosenblat JD. Targeting the immune system in the treatment of bipolar disorder. Psychopharmacology. 2019;236(10):2909–21. https://doi.org/10.1007/s00213-019-5175-x.